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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,183	12/16/2005	Anderson Joseph Ryan	056291-5223	1711

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,183	RYAN, ANDERSON JOSEPH	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 16, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/12/2006, 12/16/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/GB04/02624, filed June 18, 2004, which claims priority to foreign application GB0314097.7, filed June 18, 2003, and GB0316181.7, filed July 10, 2003. Claims 1-26 are pending in this application and examined on the merits herein.

Claim Objections

Claims 9-11 and 26 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 provide for the use of ZD6126 and another chemotherapeutic agent, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-11 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper

definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

In the interest of compact prosecution, claims 1-11 will be examined as if they claimed a method of making a medicament comprising the step of combining all of the claimed ingredients.

Claims 2-4, 6-11, 19, 20, and 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating certain specific types of cancers such as colorectal cancer, does not reasonably provide enablement for the treatment of cancers generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method for treating any cancer disorders comprising administering a combination of cytotoxic and antivascular agents.

The state of the prior art: The skilled artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen. No single chemotherapeutic drug is useful for the treatment of every case of cancer. Indeed, some types of cancer to not respond well to any known chemotherapeutic drugs. According to the Merck Manual of Diagnosis and Therapy (Reference included with PTO-892), Hepatocellular carcinomas and renal cell carcinomas are not generally improved by chemotherapy. Acute lymphoblastic leukemia, on the other hand, responds well to a number of drugs, including vincristine, anthracyclines, and aspariginases, while acute mylogenous leukemia, on the other hand, responds to fewer drugs and is usually treated with cytarabine in combination with daunorubicin or idarubicin. Breast cancer is best treated with surgery and/or radiation, but the prognosis can be improved by the addition of adjuvant chemotherapy.

Therefore the prior art does not provide an expectation that a particular chemotherapeutic agent is useful for treating all possible tumors.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: As mentioned above, no single treatment is effective for all cancers. Different cancers vary widely in their response to different chemotherapy regimens. According to the Oxford Textbook of Oncology, (Reference cited in PTO-892) "The important criteria for the tumor include its sensitivity

to cytostatic drugs, its clinical stage and its mass, the presence of measurable lesions or biochemical markers, and, finally, growth characteristics," as well as, "*In vitro* sensitivity tests have been disappointing. They predict well for resistance but are of little use for sensitivity," (p. 451, right column, second paragraph) and, "For many types of cancer the potential benefit of chemotherapy has not been demonstrated in well-designed clinical trials."

Based on the known teachings of the prior art such as that stated above, one skilled in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors: gynecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CAN, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by performing the necessary experimentation to develop an optimized dose-dense protocol for treating said cancers. Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Additionally, the currently used models of anti-cancer activity, including *in vitro* cell cultures, human xenografts, and murine allografts, are seen to be incompletely predictive of anticancer activity in actual clinical practice, as disclosed by Voskoglou-Nomikos et al. (Reference included with PTO-892) This reference discloses that human xenograft models are only predictive of anticancer activity if a sufficiently broad selection of tumor types are tested. (p. 4228, left column, last paragraph, p. 4237, left column, fourth paragraph)

The Breadth of the claims: The claimed method includes methods of treating any cancer or tumor whatsoever, regardless of the location of the tumor, the type of tissue it arose from, the size or state of progression of the disease, and the presence or absence of drug-resistance phenotypes.

The amount of direction or guidance presented: Applicant's specification includes the suggestion that the claimed compound are vascular damaging agents and are useful for broadly treating solid tumors.

The presence or absence of working examples: The only working example of successful treatment of tumors *in vivo* involves the treatment of a specific colon cell line in a mouse xenograft model.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the broad-spectrum treatment of cancer. See MPEP 2164.

The quantity of experimentation necessary: In order to use the disclosed information to practice the claimed invention for a wide range of cancers using a wide

range of drugs, a skilled practitioner of the art would develop a specific therapeutic regimen for each chemotherapy-responsive cancer. This would involve a process of optimizing and testing various regimens *in vivo* for each type of cancer being treated. In particular, dose-response curves would need to be developed for a wide variety of different cancers, and it would need to be determined which cancers are or are not appropriately treated using the claimed agents. This process would involve unpredictable experimentation which would constitute an undue experimental burden on the practitioner.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the unpredictability of the art, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all cancers.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 12-19 and 21-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis. (PCT international publication WO01/74369, Reference included with PTO-1449) Davis discloses a method of providing a vascular damaging effect, and treating cancer in a warm-blooded animal such as a human, by administering the vascular damaging agent ZD6126 in a divided or split dose. (p. 1, lines 1-7) A medicament comprising two or more doses of ZD6126, is also described. (p. 4, line 17 – p. 6, line 16) This treatment can be administered at part of a therapeutic regimen involving the simultaneous, sequential, or separate administration of another therapy such as radiotherapy (ionizing radiation) or chemotherapy. (p. 8, line 27 – p. 8, line 2) Chemotherapy agents that can be used in combination with ZD6126 include 5-fluorouracil and irinotecan. (p. 9, line 24 – p. 10 line 2) Irinotecan is the same as CPT-11, as disclosed in the chemical abstracts registry entry number 100286-90-6, which is included with form PTO-892. Therefore the compositions and kits described can also include these additional agents. Note that the intended use of the composition of instant claim 5 does not serve to distinguish it over the prior art as claim 5 merely claims a method of making a composition. The composition is expected to inherently possess the same utility as he claimed invention because it is identical in physical structure to the claimed invention. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis (PCT international publication WO01/74369, Reference included with PTO-1449) in view of Fujii. (US patent 4864021, cited in PTO-892) The disclosure of Davis is discussed above. Davis does not disclose a composition or therapeutic method involving a prodrug of 5-fluorouracil.

Fujii discloses a prodrug of fluorouracil having improved antitumor activity. (column 1, lines 1-40) These compounds are converted to 5-fluorouracil *in vivo*. (column 2, lines 4-8)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the compositions and methods of Davis using the fluorouracil prodrugs described by Fujii. One of ordinary skill in the art at the time of the invention would have recognized that the fluorouracil prodrugs can be substituted for fluorouracil in the invention of Davis, because the prodrugs are disclosed to have the same activity (anticancer activity) as fluorouracil, and is disclosed to be converted to fluorouracil *in vivo*. Making this substitution would therefore be expected to yield predictable results for the treatment of cancer.

Thus the invention taken as a whole is *prima facie* obvious.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis (PCT international publication WO01/74369, Reference included with PTO-1449) in view of Davis et al. '368. (PCT international publication WO01/74368, reference included with PTO-1449) The disclosure of Davis is discussed above. Davis does not disclose a method of treating colon cancer.

Davis et al. '368 discloses a vascular damaging method comprising administering ZD6126 in combination with other agents, similarly to Davis. (p. 1, lines 1-16) These therapeutic methods are disclosed to be useful for treating various solid tumors including colon tumors. (p. 20, lines 5-8)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the methods and compositions of Davis for the treatment of colon cancer. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Davis et al. '368 discloses that vascular damage caused by ZD6126 is useful for treating colon cancer. One of ordinary skill in the art would reasonably have expected success because the same active agent ZD6126 is used in both methods.

Thus the invention taken as a whole is *prima facie* obvious.

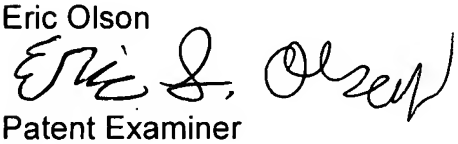
Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson

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